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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,566	02/12/2001	Bert Vogelstein	01107.00092	1623

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EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,566	VOGELSTEIN ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 08/06/2004 is acknowledged. Claims 25-32 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 27 is drawn to method of screening anticancer drug by contacting a neuroblastoma cell.

Applicant argues that the specification teaches that neuroblastoma cells may indeed have a genetic alteration which dysregulates c-myc, and further Xiaoning et al., (Exhibit A) teaches that a high expression rate of c-myc oncogene in neuroblastoma cells. These arguments have been fully considered but found unpersuasive for following reasons.

Xiaoning et al., at Table 1 teach that several neuroblastoma cells (see case 6, and 18 for example) do not express c-myc at all, and some other neuroblastoma cells express c-myc. However, Xiaoning et al., do not teach a neuroblastoma cell has "a genetic alteration which dysregulates c-myc". The specification does not teach whether a neuroblastoma cell has a genetic alteration which dysregulates c-MYC, other than the

assertion. As stated in the previous Office action, Maris and Matthay (J Clin Oncol. 1999 Jul;17(7):2264-79) teach that neuroblastoma is remarkably heterogeneous and MycN is amplified in neuroblastoma. Thus based on teachings of Xiaoning et al., and Maris and Matthay, the only way to practice the instant claimed invention is to screen which neuroblastoma cancer cell has the phenotype specified in base claim 25. It is the Office's position that screening a large quantity of clinical samples require undue experimentation. Considering the limited guidance, no working examples, the quantity of experiments involved, it is concluded that undue experimentation is required.

Claim Rejections - 35 USC § 103

Claims 25, 26, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gura (1997, Science, vol. 278, pages 1041-2), Dang (January 1999, Molecular and Cellular Biology, vol. 19, pages 1-11), and Musgrove et al., (1998, Molecular and Cellular Biology, vol. 18, pages 1812-25).

Claims 25-32 are interpreted as drawn to method of screening a candidate anti-cancer drug by contacting a cell having a genetic alteration that dysregulates c-Myc expression, followed by measuring CDK4 kinase activity of the cell, wherein a compound which inhibits CDK4 kinase activity is identified as a candidate drug with anti-cancer activity. Dependent claims 26-32 specify the types of cell with a genetic alteration that dysregulates c-Myc as being a Burkitt's Lymphoma (claim 26), a colon cancer cell (claim 28), a translocation (8;14), a genetic amplification of c-MYC (claim 30), a mutation in APC (claim 31), a truncation mutation in APC (claim 32).

Applicant argues that the Office has not made a prima facie case of obviousness because there is no suggestion or motivation in the references or in the art to combine the reference teachings. One of ordinary skill in the art would not have been motivated to combine the teachings of Gura, Muspove, and Dang to arrive at the claimed method of screening compounds to identify candidate agents having anti-cancer activity.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Gura teaches that screening potential anti-cancer drug using a variety of screening methods since 1955, often failed. In other words, Gura teaches that an agent that worked in vitro cancer cells or in vivo mice model open does not work in human clinical trials. Gura therefore, concludes that the future of cancer drug screening is toward defining molecular targets, and if the approach works, drug development would have easy way to identify promising cancer drugs (note the last paragraph of page 1042).

Gura does not teach that CDK4 or c-Myc is a molecular target.

However, Musgrove et al., teach that a proven anti-cancer drug is effect in inhibiting CD4 kinase when in vitro cancer cells are contacted. Musgrove et al., when a

breast cancer cells in vitro are contacted with progestin, "a synthetic drug in the therapy of both breast cancer and endometrial cancer" (note middle of right column at page 1812), CDK4 kinase activity is inhibited (note Fig. 3, abstract). Musgrove et al., also teach in the sentence bridging page 1812-1813 that role of c-myc and CDKs in cell cycle control has been studied. Thus, Musgrove et al., fairly suggest that CDK4 could be a molecular target since the drug inhibited CDK4 is already used for breast and endometrial cancers.

Musgrove et al., do not teach c-myc status in cancers in detail.

However, Dang teaches that the frequency of genetic alterations of c-myc in human cancers has allowed an estimation that approximately 70,000 cancer deaths per year are associated with changes in the c-myc gene its expression and that translocation (t8:14) of c-myc oncogene at chromosome 8 to 14, amplification in many human cancer including a colon cancer cell, and Burkitt's Lymphoma have a genetic alteration which dys-regulates c-MYC expression, and a mutation in a tumor suppressor APC (truncating mutation is a mutation) also causes dys-regulated c-myc expression (see Fig. 1). Note the abstract, page 1, Fig.1. Dang suggests that "therapeutic insight" might emerge by focusing on c-myc protein in cancer biology (note abstract) and teaches that c-myc and CDK4 is involved in cell cycle regulation (note page 5).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the claimed invention was made to screen candidate anti-cancer drugs using CDK4 and c-myc as molecular targets with reasonable expectation of success because Musgrove et al., teach that a clinically relevant anti-cancer agent

inhibits CDK4 and Dang teaches that c-myc is dys-regulated in many cancers. One of ordinary skill is motivated to screen anti-cancer using a molecular target because Gura teaches the other methods had not been working very well and suggests a screening method using a molecular target.

Applicant also argues that even if, for argument' sake, the references actually teach the asserted facts, none of the references teaches or suggest using a cell with an alteration which dysregulates C-MYC expression to screen for CDK4 inhibitory agents. One would have to pick and choose among the teachings of the prior art to select the particular elements of the subject claims and combine them in the manner recited. But such selective picking and choosing is not proper and certainly does not evidence a suggestion or teaching to combine.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

LARRY R. HELMS, PH.D
PRIMARY EXAMINER